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Measuring drug distribution in the critically ill patient ☆

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ABSTRACT

Critically ill patients often present with a combination of disease states and comorbid conditions that progress over a clinical course. This can manifest in physiological changes, such as fluid shifts, alterations in protein binding, and acid–base balance issues, which may in turn alter a drug's distribution, potentially towards or away from its site of action. It's vital that these factors are examined for drugs used in critical illness in varying disease states, acute and chronic in nature. Several methods have been used to study the variations in target site penetration, but few provide a feasible option to reliably measure active drug concentrations at the site of action over time. This review examines these techniques, their merits and shortcomings, generally and as they relate to use in critically ill.

Contents

1. Introduction

Critical illness is a complex heterogeneous state that varies not only by an individual's active disease states, but also temporally over the course of a patient's disease event (e.g. heart failure exacerbation, sepsis, respiratory failure). Due to this complexity, how such alterations affect pharmacotherapy efficacy and toxicity cannot be inferred without considering potential changes in pharmacokinetic (PK) and pharmacodynamic (PD) factors. Since the effect is dependent on the unbound drug concentration at the site of action, it is important to investigate how this concentration varies due to PK alterations during critical illness. In the case of infections, the target site is typically located in the extracellular or interstitial space but sometimes intracellularly [1–3]. Many techniques have the potential to be utilized to measure these concentrations. Several of these approaches might aid in optimization of dosing regimens, while select methods may be viable tools in therapeutic drug monitoring (TDM), for this population or subpopulations, such as patients receiving hemodialysis or mechanical ventilation. This

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review examines these techniques, their advantages and shortcomings, for measuring drug distribution in critically ill patients.

2. Effects of distribution changes in the critically ill

The individual complexity of each critically ill patient makes it difficult to extrapolate our understanding of a drug's distribution to a site of action, let alone generalize whole subpopulations. High variability among particular subpopulations illustrates the need for techniques for better evaluation of local drug concentrations in order to provide adequate therapy while avoiding toxicity. Pathophysiological changes, such as alterations in protein binding, pH, or fluid distribution, may or may not significantly alter a drug's distribution depending on its own molecular characteristics, such as polarity, and acidic or basic properties [4]. The flow chart in this article's graphical abstract illustrates how these physiological changes along with drug-specific characteristics might lead to a change in clinical outcome or the lack of. First, disease state or medical event-related changes occur at a physiological level. Whether or not these alterations affect a drug's distribution is dependent on the drug's specific characteristics. Even with changes in distribution, one must consider if this affects the distribution or pharmacokinetics at the site of action. Only then should consideration be given to whether significant changes in concentrations occur at the site of interest, and the resulting change in clinical outcome, be it treatment failure, drug toxicity or no change. This link to subsequent outcome is less easily predicted, but PK/PD modeling using active concentrations at the site of action may be useful to more easily evaluate whether clinically significant changes in distribution will occur. One must examine what reasonable methods are to accurately measure these concentrations.

3. Techniques for measuring distribution

This review overviews select methods including blood and saliva sampling, evaluation of skin blister fluid, microdialysis, tissue biopsy, nuclear imaging methods, and sampling of epithelial lining fluid. When applicable, examples of use of these methods in critical illness are provided.

3.1. Blood sampling

By far, serum and blood concentrations are the most commonly used measurement of drug distribution in clinical practice. Although the ease of access for sampling, availability of well-validated assays, and being generally well understood by clinicians and scientists the like make it a preferable method for drug measurement, it has obvious shortcomings. In particular, the extrapolation of blood concentrations to those at the site of action is often inappropriate and not of particular clinical relevance [5]. Exemptions are when the blood is the target site, as it is in sepsis and anticoagulation therapy, or when it is established that the blood concentrations serve as adequate surrogate for those at the target site. This may be disputed in the case of sepsis given the argument that the extracellular space is often the true source of infection for a bacteremia [2]. And while some drugs are known to be well distributed, this assumption may not hold true in light of diverse PK alterations that may occur in critical illness, making the relationship between blood and tissue concentrations unpredictable and inconsistent. Although it would be inaccurate to say that blood concentrations have no value in a clinical setting outside these situations, when considering blood concentrations, one must critically question their therapeutic value.

Although examples of monitoring drug pharmacokinetics in blood, plasma, or serum in the critically ill are extensive in the literature, examples of use in clinical practice are mostly limited to TDM of antibiotics for effectiveness (e.g. vancomycin) and toxicity (e.g. aminoglycosides). The following are select examples where blood concentrations were utilized as a means to determine if dosing was adequate in a critically ill population.

High variability in antibiotic concentrations has been observed in many studies of ICU patients. In a prospective, observational study of 24 critically ill patients with acute kidney injury receiving continuous renal replacement therapy (CRRT), a 1.9-fold to 10.5-fold variability in trough concentrations were observed for various antibiotics [6]. Minimum target trough concentrations were not attained in 15% of dosing intervals and 10% of measurements were deemed excessive relative to what was observed in healthy volunteer studies. In another study of 25 febrile hematology/oncology and ICU patients, measured meropenem plasma PK profiles were examined [7]. While there were apparent differences between PK in the febrile hematology/oncology and ICU patients and both groups exhibited high variability, the variability in meropenem PK in ICU patients was much more notable (7- to 700-fold). Lastly, Udy *et al.* measured 52 steady state trough concentrations in 48 ICU patients and found that only 58% of unbound (as calculated based on prior studies) trough concentrations attained predefined minimum targets [8]. Further analysis revealed that CrCl had a significant influence in predicting target trough attainment.

From these examples, it is apparent, a wide and often difficult to explain variability exists in blood concentrations in the critically ill. When so much variability exists, one tends to question their reliability for use as a surrogate for tissue distribution. In addition, even when the target site is the blood, it would seem unreasonable to empirically dose in a population with relatively unpredictable drug PK. Use in clinical decision-making may put patients at risk for treatment failure, resistance development, and drug-associated toxicity.

3.2. Saliva sampling

In the past, saliva sampling has been considered an easily obtained, low cost, noninvasive option for measuring unbound concentrations and as a surrogate for serum concentrations in TDM [9–11]. Unfortunately, studies have shown that saliva is an inconsistent measure for quantifying serum and tissue concentrations: in some cases, overestimating expected unbound concentrations [10,12], while in others reporting good correlation with serum concentrations [11,13]. Results can vary based on the physiochemical properties of a drug, pH, and salivary flow [1]; of which, physiological factors can be dynamic in critically ill patients. Thus it is not surprising that studies where saliva sampling is used for measuring drug distribution in the critically ill are lacking.

3.3. Skin blister fluid

Skin blister fluid is obtained by a semi-invasive procedure where negative pressure (suction) or chemical irritant (cantharides) is applied to intact skin with intent to separate dermis from epidermis to create a fluid-filled compartment, a surrogate for interstitial space [9]. While samples are easy to obtain and the technique is low in cost, it is not a reasonable approach for continuous interstitial monitoring and differences in drug concentrations have been seen with varying blister volume [14]. In addition, when done using chemical irritants, blister fluid contains inflammatory chemokines and proteins, which may not be comparable to interstitial space, given that the concentrations are not unbound, and difficult to standardize. It has been reported that blister fluid concentrations tend to overestimate expected free interstitial concentrations [10,15], while other studies show that blister fluid correlates well to plasma concentrations [12]. Some studies, in an attempt to explain higher blister fluid concentrations, allude that blister fluid may favor protein bound drugs and use of suction-induced blister fluid may minimize the potential effect of protein [15,16]. With these limitations, along with other ethical concerns in patients with skin infections or burns, it has little utility in measuring drug distribution in critically ill.